REVIEW OF ABBREVIATED AND NEW ANIMAL DRUG APPLICATION LABELING SUPPLEMENTS (NL SUBCLASS)

I. PURPOSE

This document establishes procedures for the Office of New Animal Drug Evaluation (ONADE) on how to:

- Determine if an abbreviated new animal drug application (ANADA) or new animal drug application (NADA) non-fee labeling supplement (NL) is correctly coded
- Review an (A)NADA NL Labeling Supplement
- Prepare an approval action package for an NL Labeling Supplement
- Process and finalize an (A)NADA NL Labeling Supplement

II. BACKGROUND AND SCOPE

There are two types of labeling supplements:

1. Changes being effected [(CBE) labeling supplements (CVM subclass code NL for Non-fee Labeling)], as defined in 21 CFR 514.8(c)(3), which can consist of style or design changes, and/or changes that increase safety that can be implemented immediately, prior to receipt of written notice of approval.

2. Prior approval labeling supplements (CVM subclass code NF for Non-fee Labeling), as defined in 21 CFR 514.8(c)(2), consist of revised information pertaining to effects, dosages, adverse reactions, and contraindications, the addition of an intended use, and any other labeling changes except those described in 21 CFR

514.8(c)(2). NF supplements require approval prior to distribution of the drug made using the change[1].

III. WHO IS RESPONSIBLE FOR CREATING THE APPROVAL PACKAGE?

The primary reviewer (PR) is responsible for reviewing the NL Labeling Supplement and preparing the approval package documents for the application. Team leaders (TLs) and division directors (DDs) are responsible for ensuring the accuracy of the NL Labeling Supplement approval package and that applicable policies and procedures were followed and office templates utilized. The approval package typically includes a Memorandum Recommending Approval (MRA) and supplemental approval letter. A Green Book and Animal Drugs (GBAAD) Form, Freedom of Information Summary, and a FEDERAL REGISTER (FR) update are not part of the approval package.

IV. CONFIRM THE SUBMISSION IS CORRECTLY IDENTIFIED AS AN NL LABELING SUPPLEMENT

As the PR, you will confirm that the sponsor has correctly submitted the labeling supplement as an NL Labeling Supplement. See Appendix 3 for examples of NL labeling supplements. Discuss with your TL if there are questions about whether the submission should be an NL or NF Labeling Supplement.

If the submission was submitted electronically and was incorrectly coded as an NL subclass code, you must void the submission. See P&P 1243.3011 for more detail. Then, notify the sponsor of the incorrect subclass code and ask them to resubmit their submission with the correct subclass code. If the submission was received via paper and is being accepted by ONADE in that format, you can submit a Submission Tracking and Reporting System (STARS) Correction Request Form to ask that the submission be recoded.[2] See P&P 1243.3002 for handling and rejecting paper applications and submissions.

V. PROCESSING THE NL SUBMISSION

A. Check for Completeness and Accuracy of the Submission[3]

Conduct an initial assessment of the submission (items 1 through 4, below) and determine whether it is sufficiently complete for review. If the submission is deficient on its face, issue a letter refusing to file the supplemental application within 30 days of receipt of the submission (see P&P 1243.2050).

1. Verify that the submission is assigned to the correct review division. If the submission needs to be re-assigned and you do not have STARS privileges to reassign submissions outside of your division, identify the correct division and

[1] See P&P 1243.6040 NF Supplements on the ONADE Reviewer Reference Page at Internal information redacted

[2] Link to STARS Correction Request Form Internal information redacted

[3] Note: if the supplemental application was made in paper and ONADE is accepting it, verify the signature and accuracy of the FDA Form 356v that is part of the application.

submit a STARS Correction Request form to the EDSR mailbox Internal information redacted . If you have privileges, you don't need to submit the form and can just reassign the submission.

2. Verify that the eSubmitter Submission Report includes a claim of categorical exclusion under 21 CFR 25.33 or an environmental assessment (see P&P 1243.7220).

3. Check that all proposed labeling components mentioned in the eSubmitter Submission Report are included (or attached).

4. Verify the accuracy of information provided in the eSubmitter submission report. If there are inconsistencies in the information provided in the eSubmitter submission report, the cover letter, and/or attachments to the submission, refer to ONADE's eSubmitter Policy.[4]

If any of the items above are missing or incorrect, then discuss with your supervisor if you should Refuse to Review (RTR) the supplement (see P&P 1243.2050) or request an amendment (see P&P 1243.3026).

B. Determine if Consulting Reviews are Needed

If the submission is in response to Office of Surveillance and Compliance (OSC)-initiated labeling revisions, send an informal consult to OSC (Post-Approval Review Team, HFV-216) to confirm that all requested changes have been made. Additional consulting reviews are requested on a case-by-case basis (for examples, see Appendix 1). If you are uncertain whether a division or team should be consulted on the application, either formally or informally, ask the TL of the consulting team for their input and guidance. Request consults within 5 days of receipt per the procedures described in P&P 1243.3200 and see the consulting review points of contact document on the ONADE Template SharePoint page. An informal consult may be sufficient if a comprehensive review is not required. Typically, an informal consult request consists of a few specific questions for the consulting reviewer (CR) to which they can respond succinctly via email in lieu of a formal review. Your questions for the CR and the CR's responses should be documented as a memo to file or be included in the primary review, if applicable.

C. Access the Volume 0 to Obtain the Submission Location of the Currently Approved Labeling

The Volume 0 lists the submission(s) containing each of the components of the currently approved labeling.

1. Determine if an electronic Volume 0 exists by accessing the Volume 0 libraries in SharePoint.[5] If the application is listed, access the applicable (A)NADA file number to obtain the submission number for the currently approved labeling.

[4] Link to ONADE eSubmitter Policy
Internal information redacted

[5] Link to Volume 0 library in SharePoint
Internal information redacted

Once the submission(s) containing the currently approved labeling has been identified, check STARS [Corporate Database Portal (CDP Web)] and/or the Corporate Document Management System (CDMS) to obtain copies of the labeling.

2. If an electronic copy does not exist, request the applicable paper Volume 0 from the Document Control Unit (DCU) using the Document Scanning Request Form.[6] NOTE: The Records and Information Management Team turnaround is two business days.

If supplemental labeling has been submitted and approved multiple times in the history of this product [i.e., medicated feed (Blue Bird) labels)], then check all of the submissions in STARS to determine the currently approved labeling.

VI. LABELING

A. Compare Components of the Currently Approved Labeling Referenced in the Volume 0(s) (or the Administrative Record) to the Proposed Labeling in the Supplement

Compare the submitted labeling components (e.g., package insert, immediate container, carton, Type A medicated article bag, etc.) to the currently approved labeling referenced in Volume 0 or contained in the administrative file for the (A)NADA. This comparison is to determine if the sponsor made changes other than those proposed and specified in the cover letter or described in the eSubmitter Submission Report and to determine if the proposed labeling changes are acceptable. Acceptability of the changes is based on the type and scope of the proposed change and if the labeling reflects CVM's current thinking on the contents of labeling components, such as expression of the active ingredient, listing of animal classes, location and font used for caution statements, etc. Compare the submitted labeling components to the components listed in the Volume 0. If the sponsor omitted certain components that require updates, notify the sponsor to submit the revised labeling components as an amendment to the submission. If there are questions about the acceptability of the changes, you should discuss these with the TL or DD.

We are requesting the addition of an "Approved by FDA" labeling statement based on the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (H.R. 5554).[7] These amendments added a section to the Federal Food, Drug, and Cosmetic Act (FD&C Act) that requires the addition of the statement "Approved by FDA under NADA # XXX-XXX" or "Approved by FDA under ANADA # XXX-XXX" to

[6] Link to scanning request form
Internal information redacted

[7] Link to ONADE Policy on "Approved by FDA…" labeling statements
Internal information redacted

labeling (except representative [Blue Bird] labeling) of approved new animal drugs and generic new animal drugs, respectively, by September 30, 2023. If the labeling included in the NL supplement does not include the applicable labeling statement, you should refer to the ONADE Policy 'Initial Recommendations for the Addition of Approved by FDA Statements to Labeling' found on the ONADE Policy SharePoint page for information on when and how to ask the sponsor to add the statement to the labeling.[8]

For NADA Animal Drug Availability Act (ADAA) feed combinations and for ANADA medicated feed combinations in which the effect of the supplement is related to changes in the Type A medicated article(s),[9] you should compare the submitted labeling to the approved labeling for the separately approved Type A medicated articles and to the approved labeling for the specific combination of drugs. For ANADA medicated feed combinations in which the changes are not related to changes in the Type A medicated article(s), only the comparison with the currently approved labeling for the RLNAD is needed.

The submission codes of approved labeling for the Type A medicated articles can be found in the Volume 0 under the (A)NADA numbers. The Volume 0 for the NADA ADAA and ANADA medicated feed combinations lists the submission ID of the most recently approved Blue Bird labeling. You will determine if changes made to the Type A medicated article labeling occurring after the most recently approved combination Blue Bird labeling are relevant to the combination. If so, you should request these changes be made by the sponsor and instruct the sponsor to submit revised labeling in an amendment (see P&P 1243.3026 for more information on requesting amendments).

For NL Labeling Supplements to an ANADA, you will compare the proposed new generic labeling to the currently approved RLNAD labeling, as well as to the currently approved generic labeling. Each of these is referenced in their respective Volume 0 or in the (A)NADA administrative file.

Steps for comparison of the labeling:

- Review the eSubmitter Submission Report and cover letter for a summary of the proposed labeling changes. If discrepancies exist between the two, the PR should contact the sponsor for clarification.
- Note the differences between the currently approved labeling (in Volume 0 or administrative record) and the proposed labeling with a side-by-side comparison. Record substantial differences in the MRA or review.
- Discuss any questions about the changes to or differences in the labeling with the TL or DD.

[8] Link to ONADE Policy on approved by FDA statements
Internal information redacted

[9] Examples include changes in feeding directions, approved species, etc.

B. Compare Changes to the Regulations

Compare the electronic Code of Federal Regulations (eCFR) citation Internal information redacted under Title 21 CFR Section 520-558) to the proposed labeling. If there is a substantive discrepancy with the eCFR, determine whether the proposed labeling or the eCFR is correct by checking the history of the (A)NADA in the administrative record. Document any substantive discrepancies in the MRA. If the eCFR is incorrect, email the CVM Policy and Regulations Team (HFV-6) to request revisions using the CFR Batch Changes Outlook template.[10] Attach the email as part of your MRA. NOTE: The Policy and Regulations Team has six months to update the CFR, so request only minor changes this way. If major or significant changes to the CFR are required, email HFV-6 directly (not using the template) to request the changes be implemented more rapidly. If significant research was required to verify correctness of labeling and the CFR, add a note to the Volume 0 that references the appropriate files to check or cite a review that documents the details of your comparison.

C. Determine if the Sponsor Has Addressed Any Outstanding Labeling Changes Requested by OSC

OSC's Division of Surveillance (DS) maintains the Drug Event Reporting (DER) database containing current OSC requests for labeling changes. Find the DER database through the CDP Portal. Determine whether the outstanding labeling change requests identified in the DER database are incorporated in the labeling for the pending supplement. The instructions for accessing the DER are provided in the document found in the ONADE SOP on the process for accessing the Drug Experience Reporting database.[11] If necessary, contact OSC (Post-Approval Review Team, HFV-216) to get more information.

If the application contains labeling with OSC-initiated labeling changes, use the OSC-initiated labeling changes email template to email OSC and request that the reviewer provide the labeling language for the Green Book Monthly Update. Prepare a Green Book and Animal Drugs @ FDA (GBAAD) form as described in P&P 1243.3801.

D. Comparing Supplemental Application Information to Animal Drugs @ FDA (ADAFDA)

Compare the information in the submission to the information in ADAFDA. If the information in the submission related to the ADAFDA has changed, note the changes in the Animal Drugs @ FDA section of the MRA. When the submission is finalized, the Business Informatics Team will check the MRA and, if applicable, make changes to the ADAFDA database. See P&P 1243.3801, 1243.3900, and P&P 1243.5741.

[10] Link to ONADE Template Page in SharePoint. Scroll down to Outlook Template section Internal information redacted

[11] See ONADE SOP 1243.120.001 ONADE Process for Accessing the Drug Experience Reporting (DER) Database to Perform Status Checks

E. Determine If We Can Approve the NL Supplement

1. If the NL Labeling Supplement can be amended, proceed to Section VI.F.
2. If the NL Labeling Supplement can be approved without amendment, proceed to Section VII.A.
3. If the NL Labeling Supplement cannot be approved, proceed to Section VII.B.

F. If the Supplement Can Be Amended

If the observed deficiencies in the NL Labeling Supplement can be corrected in an amendment:

- Email the sponsor and provide the requested labeling changes and a due date for their amendment, see P&P 1243.3026.
- If the applicable "Approved by FDA…" statement is not already included on the labeling and the submission needs to be amended for any other reason, include in the amendment request applicable language from the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling, Section X, recommending the addition of the statement.
- Prepare a Memo to File or Review or attach the email as an appendix to the MRA to document correspondence with the sponsor.

See Appendix 2 for more information on what changes may require an amendment.

If we can approve the application as amended, proceed to Section VII.A; otherwise proceed to Section VII.B.

VII. FINALIZING THE SUBMISSION

A. When We Are Approving the Labeling Supplement

If the labeling is found to be acceptable for approval, update the Volume 0 accordingly (P&P 1243.3810) and prepare the MRA (P&P 243.5741) and an (A)NADA Supplemental Approval Letter. Templates are located on the ONADE Template Page in SharePoint: In the MRA, discuss any additional significant differences between the proposed and currently approved labeling, other than those specifically requested by the sponsor.

- If the applicable "Approved by FDA…" statement is not already included on the labeling, include applicable language from the approval letter template to request the addition of the statement in final printed labeling, a general correspondence submission for Blue Bird labeling, or future supplemental applications.
- Discuss any additional future changes with the TL and determine if the sponsor should be contacted to make them aware of the changes or if the changes, we

want them to make should only be included as comments in the approval letter.

- In the MRA, state if there are changes to the labeling that the sponsor should make in a future supplement. Send an email to DCU2mailbox@fda.hhs.gov, copying the TL of the Post-Approval Review Team (HFV-216) with the subject line "Prospective Changes" and list the pertinent drug information and the requested changes. HFV-216 will then send the sponsor a letter. Attach the email as an appendix in the MRA.

For more information on approval letter comments and prospective changes, see Appendix 2.

After completing the above items, proceed to Section VII.C.

B. When We Are Not Approving the Labeling Supplement

If we are not approving the supplement, prepare an incomplete letter and a review to document and describe the unacceptable labeling changes found in the current labeling and/or changes required to make the labeling acceptable.

If the applicable "Approved by FDA…" statement is not already included on the labeling, include in the incomplete letter applicable language from the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling, Section X, to ask that the appropriate statement be added to the labeling by September 30, 2023.

When you have determined we cannot approve the labeling, do NOT update the Volume 0 for that application.

C. Assembling and Routing the Final Action Package for the Submission in Appian

Once the draft final action package has been prepared, regardless of whether we are approving the supplement or not, work with the TL and DD to complete the review of the package so that the package is signed-off in Appian by day 60. The Appian concurrence chain includes the you (the PR), TL, and DD. NOTE: These types of submissions do not require a request for a Quality Control consulting review from the Quality Assurance Team.

In the final action package, choose the appropriate final action code. Below are the most common final action codes for NL submissions. Speak to your TL if you are unsure which code is correct. (See P&P 1243.5741.)

REFUSE SUP – Refuse to file supplemental application; letter sent
INC APP – Incomplete application; letter sent
SUP MIN LD – Minor supplement approved date of letter; letter sent

You should note in the STARS Review Summary the effect of the supplement. Finalize and load the submission and all accompanying documentation into Appian based on division policies. Refer to P&P 1243.3005 and 1243.3030 for creating clean electronic files and preparation of the final action package.

If the labeling supplement is being approved and contained final printed labeling (FPL), notify OSC by checking the appropriate box on the Appian Additional Actions screen. This will generate an automatic email to notify OSC that ONADE has received FPL to aid in OSC's maintenance of the DER database.

D. Other Administrative Tasks to Complete After the Final Action Package Closes When the Supplement is Approved

Update the Volume 0. See P&P 1243.3810 entitled "Creating and Maintaining a Reference Copy of the Currently Approved Labeling for an Application (Volume 0)."

VIII. REFERENCES

Statutes

Rehabilitation Act

29 U.S.C. 794d

§508

Code of Federal Regulations (Title 21)

Part 514 – New Animal Drug Applications

Part 514.8 – Supplements and other changes to an approved application

Guidance for Industry (GFI)

GFI #240 - Proprietary Names for New Animal Drugs

GFI #191 - Changed to Approved NADAs – New NADAs vs. Category II Supplemental NADAs

CVM Program Policy and Procedures Manual- ONADE Reviewer's Chapter

1243.2050 – Refuse to File and Refuse to Review

1243.3002 – Handling and Rejecting Paper Applications and Submissions

1243.3005 – Creating Clean Electronic Files

1243.3011 – Voiding Submissions and Discontinuing the Review of Pending Submissions and Applications

1243.3026 – Assessing Submission Quality and Amending and Resetting the Clock on Submissions

1243.3200 – Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission

1243.3801 – Completing the Green Book and Animal Drugs @ FDA (GBAAD) Form

1243.3810 – Creating and Maintaining a Reference Copy of the Currently Approved Labeling for an Application (Volume 0)

1243.3900 – Updating the Animal Drugs @ FDA Website and Green Book

1243.5741 – Memorandum Recommending Approval (MRA) for Original and Supplemental (Abbreviated) New Animal Drug Applications (A)NADA

1243.6040 – Review of Abbreviated and New Animal Drug Application 60- and 180-day Non-fee Prior Approval Labeling Supplements (NF Subclass)

1243.7220 – Processing Environmental Impact Submissions for New Animal Drugs

ONADE Standard Operating Procedures and Scientific Reference Documents

1243.120.001 - ONADE Process for Accessing the Drug Experience Reporting (DER) Database to Perform Status Checks

ONADE Office Policy Page

Initial Recommendations for the Addition of Approved by FDA Statements to Labeling

IX. VERSION HISTORY

August 23, 2007 – Original version

March 12, 2008 – Revised to remove hotlinks that did not work.

June 16, 2009 – Revised to reflect that OSC maintains a DER database and that if ONADE wants future labeling changes alert OSC using the DCU2 Outlook mailbox. Copies of emails to DCU2 should be included in the approval package.

November 10, 2009 – Revised the section regarding supplements that can be approved to remove redundancy.

October 22, 2012 – Revised to include electronic review procedures and limit to NL labeling supplements.

June 22, 2016 – Updated to current format, added background information, slight reorganization of information, and redaction of internal information.

April 10, 2019 – Updated to conform with changes to the newly prepared NF Labeling Supplement P&P (1243.6040), to reflect current functionality of the Appian Additional Action Screen, and to add instructions on when and how to ask for addition of "Approved by FDA…" statements to labeling.

June 22, 2020 - Updated all internal links for SharePoint sites because FDA has migrated this information to a new version of SharePoint.

August 25, 2020 – Updated to replace the link to the ONADE template page and the Document Scanning Request form that now has new locations.

September 17, 2020 – Revised to include instructions related to applications containing OSC-initiated labeling changes.

July 9, 2021 – As a result of an audit of NF and NL supplements, it was determined more clarity with regard to what is an NF or NL supplement was needed in the associated P&Ps on the subject (i.e., 1243.6020 and 6040). This document was therefore revised to include an appendix with NL and NF labeling supplement examples. Section V. B. was updated to note that if the labeling changes were requested by OSC, there should be an informal consult sent to OSC's HFV-216 to confirm all changes requested have been made. Updated to fix some punctuation errors

APPENDIX 1. EXAMPLES OF WHEN TO REQUEST A CONSULT (FORMAL OR INFORMAL)

Type of Question	Who to Consult
New or modified trade dress	OSC (HFV-216)
Verification of USP monograph or established name	DMT
Medicated feed formulation change and/or labeling change	DMT (HFV-141) OSC (HFV-226)
Potential promotional statements in the labeling	OSC (HFV-216)
Tradename change	OSC (HFV-216)
All label change supplements initiated by the Division of Surveillance	Contact the requesting team in the Division of Surveillance

Note: For medicated feeds ONADE will schedule a meeting with OSC to discuss proposed labeling changes. If the labeling is acceptable, OSC will not prepare a review. If there are changes that must be made or should be made to conform to the CVM guidance on Blue Bird labeling, Division of Animal Feeds will provide comments in a written review. They commit to a 30-day turnaround on a written consult.

APPENDIX 2. DESCRIPTION OF AMENDMENTS VS. APPROVAL LETTER COMMENTS VS. PROSPECTIVE CHANGES

1. Amendment (Required) Changes: Request a required amendment to the submission for any change that would pose a public health risk if not immediately implemented. If the sponsor does not make these changes, the supplement is incomplete.

   Examples: Errors in dosing instructions or mixing/feeding directions, lack of warning or caution statements, location and font used for caution statements

   If the applicable "Approved by FDA…" statement is not already included on the labeling and the submission needs to be amended for any other reason, include in the amendment request applicable language from the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling, Section X, recommending the addition of the statement.

2. Approval Letter Comments: Include in the approval letter only comments related to minor typographical or style-type changes that: 1) do not call into question the approval, 2) are easily fixed with minimal chance for the sponsor to introduce errors, and 3) would not pose a public health risk if they were never implemented.

   If the applicable "Approved by FDA…" statement is not already included on the labeling, include applicable language from the approval letter template to request addition of the statement in final printed labeling, a general correspondence letter for Blue Bird labeling, or future supplemental applications.

3. Prospective Changes: Major changes that are required but cannot be addressed during the timeframe of the submission review AND do not pose an immediate health risk.

   Examples: Expression of the active ingredient for products where the labeling does not match the drug product monograph, listing of animal classes

APPENDIX 3. EXAMPLES OF NL AND NF LABELING SUPPLEMENTS

Table 1: NL Labeling Supplement Examples (NADA)

NL Examples (NADA)
Correction of spelling errors
Revised drug product name (e.g., due to USP monograph or per GFI #240[12])
Changed artwork codes or artwork revisions
Minor color/graphic changes (e.g., changed border or text color, logo, font size, animal picture, worm or parasite icons)
Minor formatting changes (e.g., relocation of text or changing presentation of text from a horizontal box to a vertical box)
Changed (or added) warning statements requested by OSC
Updated website for reporting adverse events
Updated sponsor name, address, trademark or copyright statements, drug label codes, or country of origin
Updated storage information statements
Revisions to align with CVM's current thinking on labeling components
Revised target animal classes to fit current nomenclature (Appendix III, GFI #191[13])
Updated revision date
Updated patent information
Revised target bacteria name
New labeling component (e.g., shipping label)
Added the "Approved by FDA" statement
Deletion of false, misleading, or unsupported intended uses or claims for effectiveness (typically an OSC recommendation)

[12] Guidance For Industry #240, "Proprietary Names for New Animal Drugs"

[13] Guidance for Industry #191, "Changes to Approved NADAs- New NADAs vs. Category II Supplemental NADAs"

Table 2: NF Labeling Supplement Examples (60-Day and 180-Day Pioneer NFs and 60-Day and 270-Day Generic NFs)

NF Examples (NADA)	NF Examples (ANADA)
New labeling component (e.g., new carton or a new puppy pack presentation) that may require an OSC labeling consultation	Addition of a species, class, subclass, or indication (usually as a result of expiration of patent or marketing exclusivity provisions)
Font size revisions that are potential safety issues (e.g., drug product strength size changed from 12 pt font to 6 pt font)	Change in withdrawal period(s) and/or residue warning(s)
Drug product return to market	Change in proprietary name
Change in mixing and/or feeding directions for a medicated feed	Minor changes to feeding and mixing directions for a medicated feed
Creation of combination blue bird labeling	Changes in trade dress (including addition of a labeling presentation)
Changes that reflect a transfer of ownership and/or sponsor information (that may require right of reference information)	Correction of errors in species, class, subclass, or indication (due to RLNAD error)
Change in the active drug ingredient concentration (e.g., medicated feeds)	
Added adverse event and/or safety information (sponsor initiated)	